Advances in Public Health Genomics. Session 4: Can multiple genetic variants improve risk assessment and disease prevention?

Sholom Wacholder

Rockville, January 28, 2009

Two goals in 20 minutes

- Focus on breast cancer risk

1. Empirical evaluation of effect of adding SNPs to Gail model

2. Discussion of appropriate standard

Importance of risk assessment

- Risk assessment is key tool in clinical decision making
- Decisions based on disparate criteria can be integrated into a single risk score
- *Positive* and *negative* predictive values
  - Over future time period
    - E.g., 5 years
  - *PPV*: "Is my risk high enough to justify aggressive intervention?"
  - *NPV*: "Is my risk low enough to provide reassurance that more aggressive intervention is not needed?"

BCRAT as example of risk assessment

- Gail score integrates
  1. Genetics
     - family history of breast and ovarian cancer
  2. Markers of disease progression
     - number of breast biopsies
     - hyperplasia
  3. Reproductive history
     - age at first birth
  4. Hormonal milieu
     - age at menarche
- Based on info in patient chart!

Does adding SNPs improve the Gail model?

- More direct measure of genetics
- All identified risk alleles either:
  - From GWAS: Low penetrance
    - Small additional risk conferred
  - From linkage studies
    - Very rare
- Would require DNA
- Would cost money, at least in short term

How much does DNA help?

- Standard measure is Area Under the Receiver Operator Characteristic (ROC) Curve (AUC)
- Empirical data on AUC

Added AUC for breast cancer risk model from adding 7 SNPs

- Empirical data
  - From CGEMS
  - Thomas, in press, NG
- 5 studies
  - 4 US cohorts
    - Nested case-control
  - 1 case-control in Poland
- Analyses here based on
  - Age 50 to 79
  - 3923 cases
  - 4086 controls
  - "development set"
  - Additional data forthcoming

Study	Cases	Controls
WHI	1551	1557
Poland	907	1023
PLCO	650	633
Nurses	543	519
CPS II	272	354

AUC details

- Use external allele estimates
  - Pharoah, 2008
  - 7 SNPs
  - Equal additional relative risk at each SNP for
    - carrying 2nd risk allele vs. only 1 risk allele *and*
    - carrying 1 allele vs. none
  - Joint effects of 7 SNPs are multiplicative

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Douglas F. Easton, Ph.D., and Bruce A.J. Ponder, F.R.S.

N Engl J Med 2008;358:2796-803.

Table 1. Established Common Breast-Cancer Susceptibility Alleles.*

dbSNP No.	Gene†	Chromosome	Risk-Allele Frequency‡	Relative Risk per Allele‡	Fraction of Total Variance in Risk Explained§ %	Population Attributable Risk§	Study
rs2981582	*FGFR2*	10q	0.38	1.26	1.7	19	Easton et al.,[26] Hunter et al.[27]
rs3803662	*TNRC9, LOC643714*	16q	0.25	1.20	0.9	10	Easton et al.[26]
rs889312	*MAP3K1*	5q	0.28	1.13	0.4	7	Easton et al.[26]
rs3817198	*LSP1*	11p	0.30	1.07	0.1	4	Easton et al.[26]
rs13281615	None known	8q	0.40	1.08	0.2	6	Easton et al.[26]
rs13387042	None known	2q	0.50	1.20	1.2	19	Stacey et al.[28]
rs1053485	*CASP8*	2q	0.86	1.13	0.3	20	Cox et al.[25]

N Engl J Med 2008;358:2796-803.

Score for each case and control

- **Score for each case and control**

$$S_i = \sum_{k=1,\cdots,7} \beta_k A_k$$

  - β_k **is the log of relative per-allele relative risk in Pharoah**
  - A_k **is the number of risk alleles at SNP i.**

$$AUC = \sum_{i \text{ for } cases} \sum_{j \text{ for } controls} \frac{\mathrm{Ind}(S_i > T_j) + \mathrm{Ind}(S_i == T_j)/2}{N_{case} N_{control}}$$

  - S_i **index** N_{case} **cases**
  - T_j **index** $N_{control}$ **controls**

Potential improvement of risk models

- Combine into single model
  - SNPs
  - Factors from Gail model
    - Any duplication
- Adding new factors
  - Mammographic density
  - More SNPs?
- Use of functional alleles instead of markers
  - Remove attenuation in estimates of risk
- Describe joint effects of all factors
  - Is multiplicative assumption adequate
    - Alternative models will be hard to validate as number of factors increases
    - Little empirical evidence

Is AUC the appropriate measure?

- AUC measures discrimination
  - Separation of cases from controls
- Discrimination is necessary, but not sufficient, for a good risk model
  - Hard to translate AUC -> value
    - Case frequency: 60%
    - Control frequency: 40%
      - OR=2.25
      - AUC=60%
- Superior alternatives to AUC

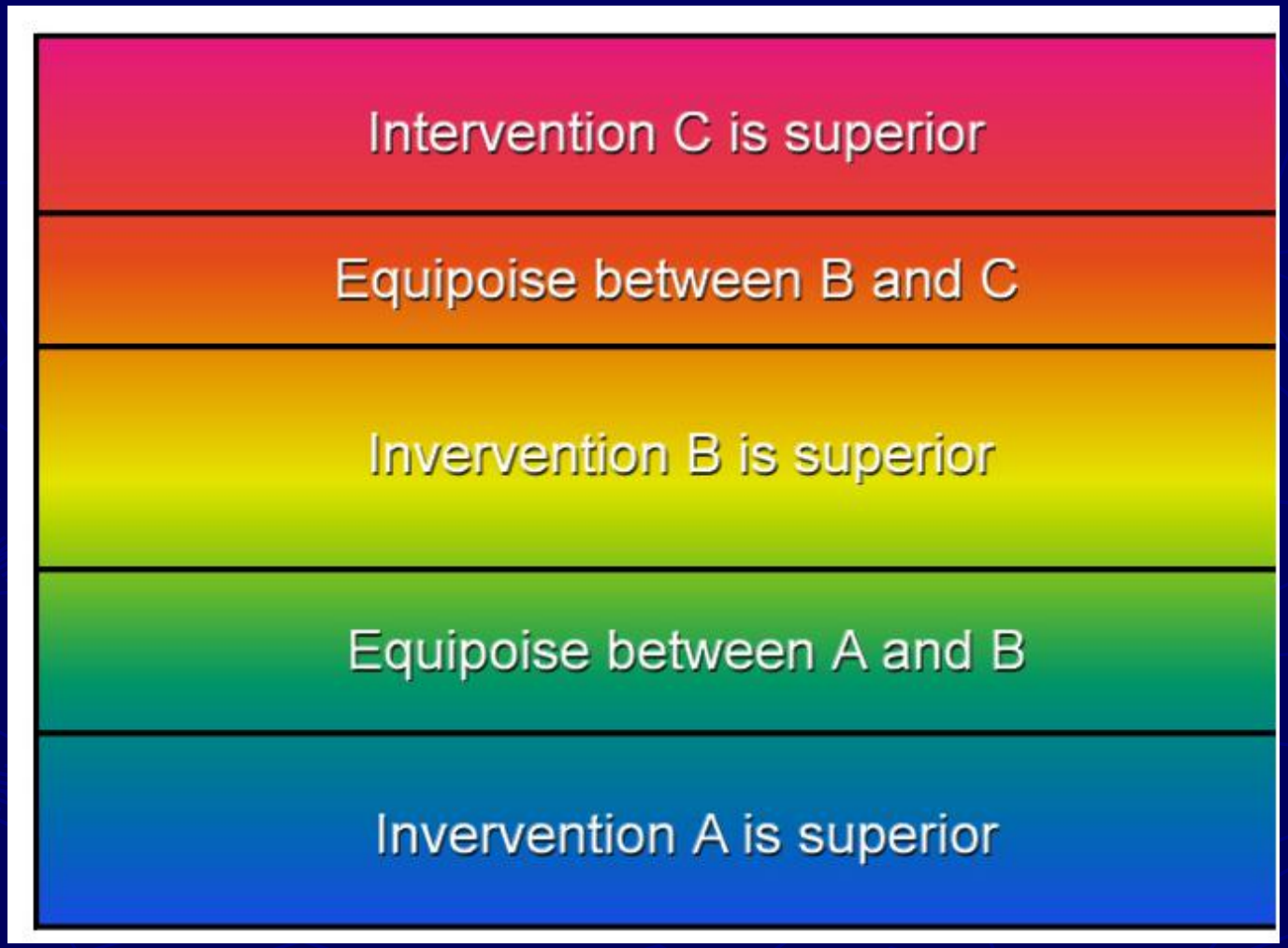
Five-year risk from BCRAT	Five-year risk from BCRATplus7 (Slide from MG)					
	<1.0%	1.0 to <1.5%	1.5 to <2.0%	2.0 to <2.5%	≥2.5%	Total
<1.0%	29.4	8.0	0.6	0.0	0.0	38.0
1.0 to <1.5%	15.4	21.6	6.0	0.9	0.1	44.0
1.5 to <2.0%	0.2	3.0	3.7	1.9	0.9	9.7
2.0 to <2.5%	0.0	0.6	1.8	1.6	1.3	5.3
≥2.5%	0.0	0.0	0.2	0.4	2.3	2.9
Total	45.0	33.2	12.3	4.8	4.6	99.9

Cross-classification in Percent at the Threshold of 2% (from MG)

		BCRATplus7		Total
		<2%	≥2%	
BCRAT	<2%	87.9	3.8	91.7
	≥2%	2.6	5.6	8.2
	Total	90.5	9.4	99.9

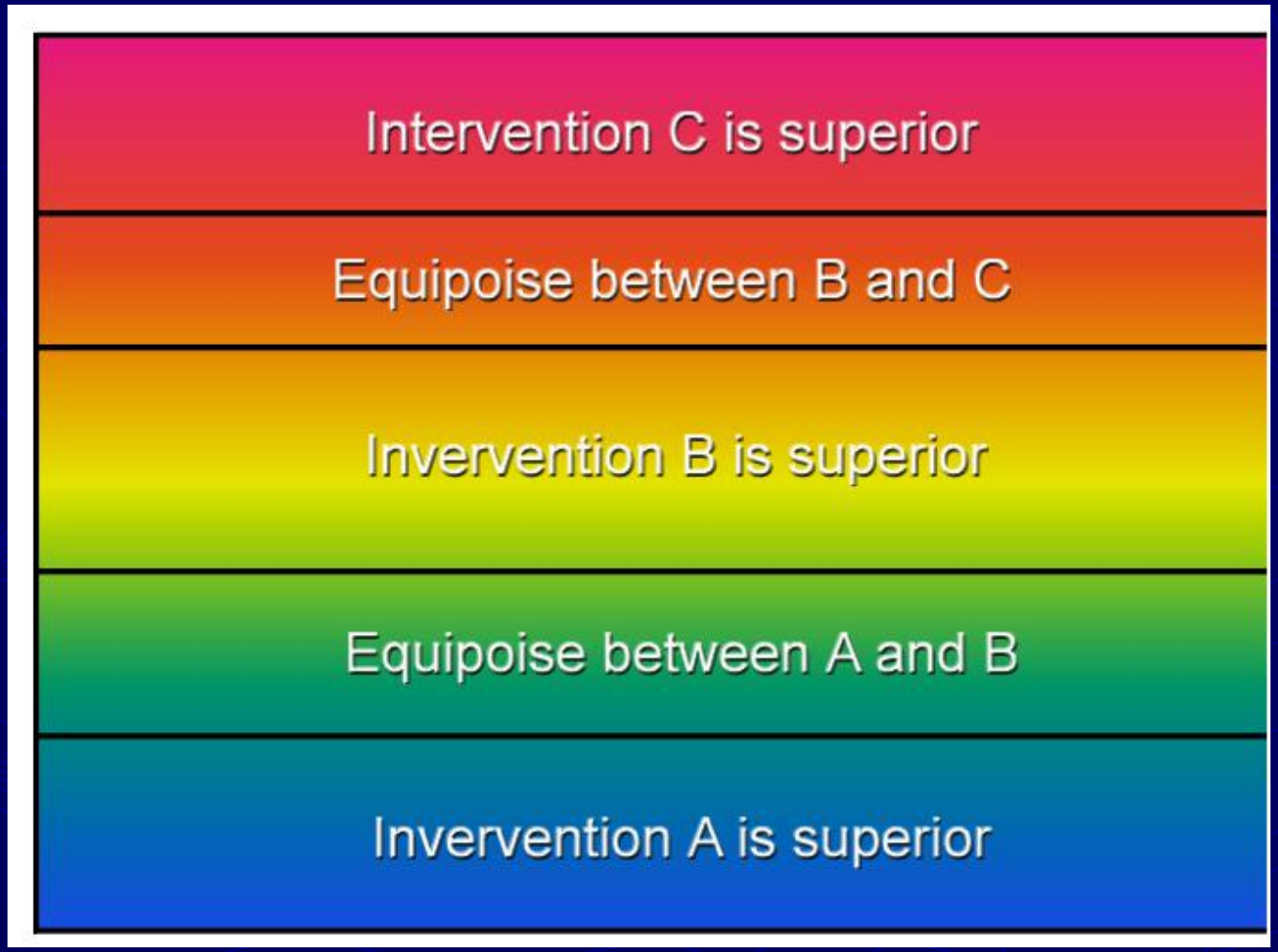
Regions of Preference and Equipoise for 3 Interventions:

A is benign; B is more aggressive; C is most aggressive



Regions of Preference and Equipoise for 3 Interventions:

A is benign; B is more aggressive; C is most aggressive



Premise

- Evaluate risk assessment models as we evaluate any clinical test

Implications

- Risk thresholds focus on performance
  - Can improved risk model improve practice?
- But thresholds necessarily arbitrary now

Choosing thresholds

- Based on good data on risk:
  - We are getting there…
- Need good data on costs and benefits of interventions
- →get us to thresholds based on equipoise between interventions

Evaluation of risk model as a clinical test

- % of women whose recommendation changes with the use of risk model
- Average improvement in benefit less cost from use of intervention
- Incorporate costs of calculating risk model

What we need

- Set of intervention options
  - Screening modes and intervals
    - Digital MRI
    - Triennial mammography
    - Annual mammography
  - Hormone-based prevention
    - Tamoxifen
    - Raloxifene
  - Surgery
    - Oophorectomy
    - Mastectomy
- Risk levels at which one intervention is clearly superior to all others
  - Benefit less costs

Will adding SNPs help?

- Costs of adding SNPs
  - Patient chart vs. DNA
  - Complexity of model irrelevant
    - Automation
- How much improvement in performance?
  - i.e., patient outcome
  - Individualized *Benefit less Cost*

Conclusion

- We need more evidence of improvement of outcomes from assignment of women to intervention based on
  - Gail model
  - Gail model plus SNPs

Acknowledgements

- DCEG
  - CGEMS: Stephen Chanock,, Robert Hoover, Kevin Jacobs, Gilles Thomas
  - PBCS: Louise Brinton, Montserrat Garcia-Closas, Mark Sherman,
  - PLCO: Patricia Hartge
  - Statistics: Mitchell Gail, Ruth Pfeiffer
- ACS (CPS II): Jeanne Calle, W. Ryan Driver, Heather Feigelson, Michael Thun
- Harvard (NHS): David Cox, David Hunter, Susan Hankinson, Peter Kraft
- DCP (PLCO): Christine Berg
- Cambridge (PBCS): Jolanta Lissowska
- UCLA (WHI): Rowan Chlebowski
- FHCRC (WHI): Charles Kooperberg, Rebecca Jackson, Ross Prentice
- IMS: Dennis Buckman, Peter Hui